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A technique for excision of abdominal and pelvic neuroblastomas

EDWARD KIELY

Department of Paediatric Surgery, Great Ormond Street Hospital for Children, London, UK

ABSTRACT

INTRODUCTION As neuroblastomas usually envelope major vessels, excision poses a significant technical problem.

PATIENTS AND METHODS Over a 22-year period, 234 infants and children have undergone attempted surgical excision of abdominal or pelvic neuroblastomas using a consistent surgical approach. This entails a systematic dissection of the involved vessels prior to removal of the tumour.

RESULTS Macroscopically complete or near complete tumour clearance was achieved in 89% of cases. Three aortic injuries occurred which required repair.

CONCLUSIONS The described technique is safe and reproducible and allows tumour clearance in the majority of affected children.

KEYWORDS

Neuroblastoma – Surgery – Surgical technique

CORRESPONDENCE TO

Edward Kiely, Consultant Paediatric Surgeon, Great Ormond Street Hospital for Children, Great Ormond Street, London WC1N 3JH, UK
E: edwardkiely@mac.com

Neuroblastoma is the most common abdominal malignancy of childhood, occurring in about 1 in 10,000 children.[1] These tumours arise in primitive elements of the sympathetic nervous system and consequently are seen in the adrenal medulla as well as sites of sympathetic ganglia, mainly along the sympathetic chains.

In general, these tumours are highly malignant and the majority (about two-thirds) present with locally advanced or metastatic disease.[2,3] These tumours are staged in accordance with agreed staging criteria, of which the most commonly used is the International Neuroblastoma Staging System (INSS).[3]

Children with stage 1 disease have localised tumour confined to the organ of origin, and can be macroscopically excised. Those with stage 2 disease have tumour which has spread outside the organ of origin or have ipsilateral involved lymph nodes or those where macroscopic clearance was not achieved. Children with stage 3 disease are those whose tumours arise in the mid-line or cross the mid-line or those with contralateral involved nodes. Stage 4 disease refers to those who have distant metastases, predominantly skeletal.

In addition, a number of biological markers – MYCN amplification, 1p deletion, 17q gain – have further defined inherent tumour behaviour. Tumours which show these features are more aggressive and are associated with reduced survival.[4] A number of biochemical markers in the serum also help to define tumours with more aggressive behaviour – elevated levels of lactate dehydrogenase (LDH), neuron specific enolase (NSE) and ferritin denote a worse outcome. In general, poor biological and biochemical profiles are associated with advanced clinical stage.

It has also been clear for many years that age at diagnosis affects the prognosis. Infants (those less than 12 months old) generally have a more favourable biological profile but, even allowing for this, have a better prognosis than older children.[5] Finally, site of the primary tumour will also influence the outcome. Those with thoracic or pelvic primary tumours have a substantially better outlook than those with an abdominal primary tumour.[6]

Until recently, the overall mortality of neuroblastoma was in excess of 85%, but survival has now improved overall to about 50%.[7] For those with locally advanced disease at presentation, survival approaches 80% for those who have undergone complete resection but falls to 30% in those in whom resection was not possible.[8]

The place of surgery in the management of children with metastatic disease remains controversial.[9,10] Most tumour

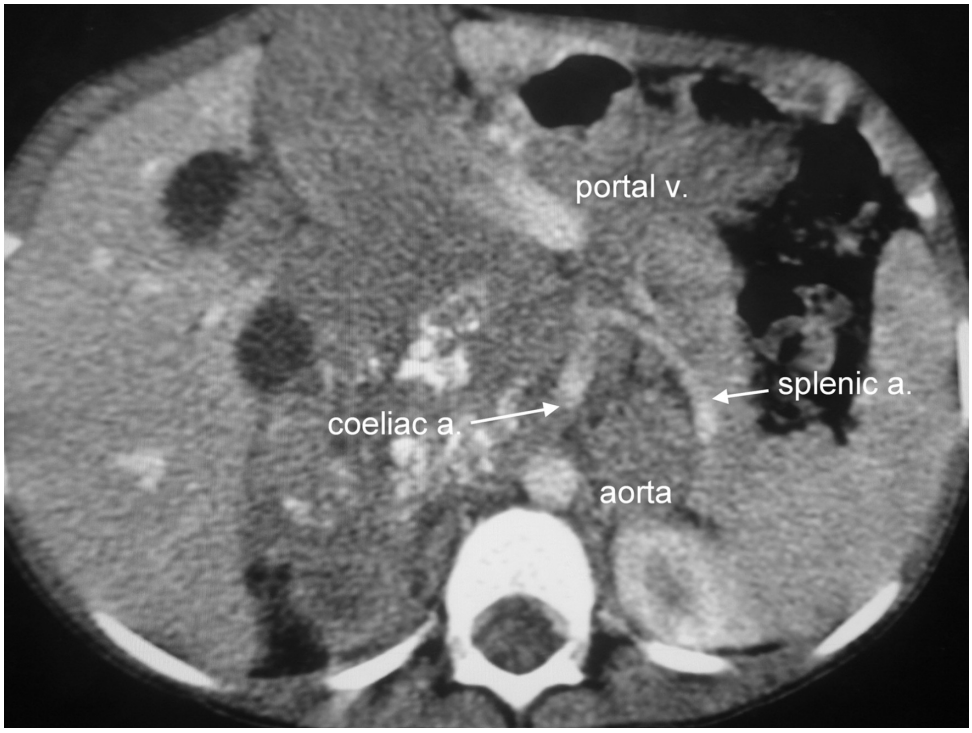

Figure 1 Pre-treatment CT scan of abdominal neuroblastoma.

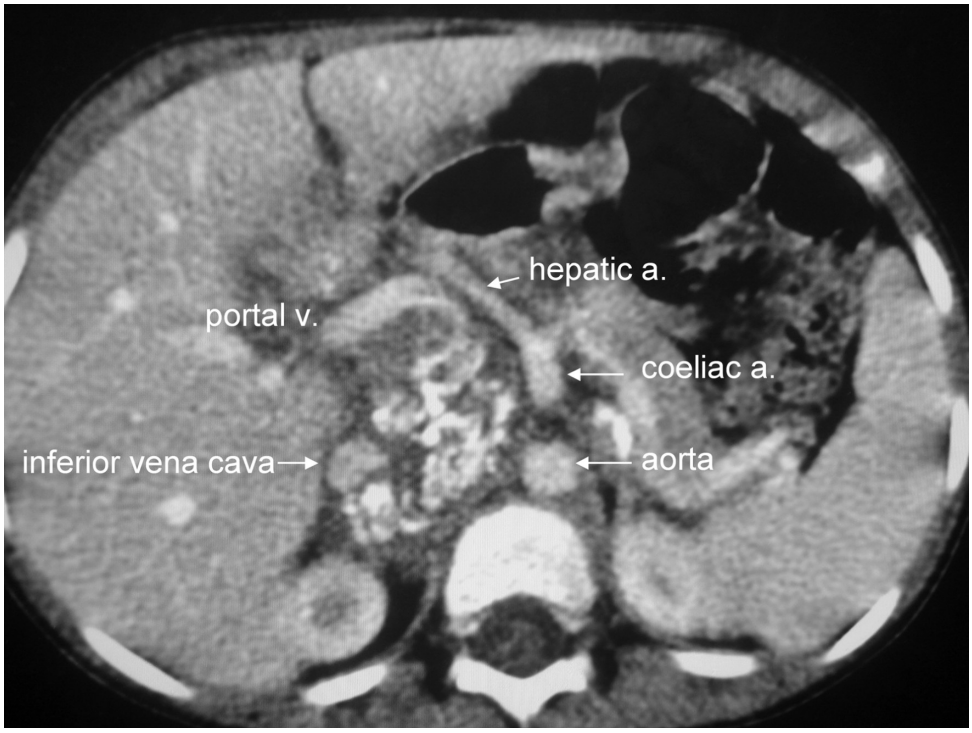

Figure 2 Post-chemotherapy CT scan showing tumour shrinkage.

treatment protocols include attempted excision of the primary tumour after chemotherapy ablation of metastatic disease. Over the past 30 years, chemotherapy protocols have been developed which can usually ablate metastatic disease and shrink the primary tumour. This shrinkage may be clearly seen on serial scanning (Figs 1 and 2). The post-chemotherapy scan shows tumour shrinkage with increased calcification but tumour persists on both sides of the aorta. Post-chemotherapy tumours are harder in consistency, more fibrotic and substantially less vascular than at the time of presentation. As a result, there is a realistic opportunity to attempt complete macroscopic excision. As these tumours envelope major blood vessels, excision presents a technical challenge.

There is little guidance in the surgical literature to suggest how tumour removal might be accomplished. Occasional reports describe misadventure and, from discussion with colleagues, it is clear that major vessel injury is perceived as a substantial risk of such surgery.[11]

The surgical technique described here was developed to minimise the risk of vascular injury and to achieve optimal tumour clearance.[12]

Patients and Methods

Over the 22-year period from 1983 to 2005, 255 infants and children with neuroblastoma have undergone attempted tumour excision. Of these, 207 (81%) had an abdominal primary tumour, 31 (12%) a thoracic primary tumour and 17 (6.6%) had pelvic disease. The sites of disease in those with abdominal and pelvic tumours are shown in Table 1. It is clear that the adrenal is the commonest site of disease overall but a substantial number of the remainder with abdominal disease have tumour closely applied to, or enveloping, the aorta.

Of those with pelvic disease, about half were presacral and the remainder were sited on the lateral wall of the pelvis.

Table 2 shows the disease stage at the time of presentation. As can be seen, almost 60% had metastatic stage 4 disease at the time of diagnosis.

Surgical technique

The aim of the technique is to display all the major vessels as they traverse the tumour. *En bloc* excision is clearly not an option when vascular encasement is present.

Once the vessels are free, the different segments of tumour are removed piecemeal.

The basis of the operative technique is that these tumours do not usually invade beyond the tunica adventitia of major blood vessels. Consequently, a plane of dissection may be developed between tumour and tunica media. This is most easily accomplished using a scalpel.

Table 1 Sites of primary disease

Sites of primary disease	*n*	(%)
Abdominal	207	(81)
Adrenal	137	(54)
Para-aortic	17	(6.6)
Pre-aortic	22	(8.6)
Para-vertebral	28	(10.9)
Pelvic	17	(6.6)

There are three phases to the procedure – vessel display, vessel clearance and tumour removal. The first phase is to display part of the wall of each of the vessels which traverses the tumour, in continuity. The vessels are subsequently cleared circumferentially and mobilised from the tumour, after which the tumour may be removed. As with any operation, these phases are not absolutely distinct during the course of a long operation.

Surgery is undertaken under full intubated general anaesthesia with arterial and venous pressure monitoring. A urinary catheter is also inserted. Over the past 15 years, epidural anaesthesia has been employed in all patients who do not have spinal involvement.

For those with an abdominal primary tumour, the abdomen is opened through a transverse supra-umbilical incision. Full laparotomy is performed before evaluating the extent of disease. On whichever side the tumour arises, the colon is reflected medially to display the tumour. On the left side, the spleen and pancreas are also mobilised and all the viscera are placed in an intestinal bag. The use of a table-mounted retractor is of considerable benefit.

Dissection is commenced distally below the lower limit of the tumour. This usually means the common or external iliac vein on the right side or the corresponding artery on the left side. The surgeon and assistant each pick up the tunica adventitia of the blood vessel and this is then incised along the middle of the vessel to enter the subadventitial

Table 2 Tumour stage at diagnosis

Stage at diagnosis	*n*	(%)
Stage 1	6	(2)
Stage 2	42	(16)
Stage 3	51	(20)
Stage 4	150	(58.8)

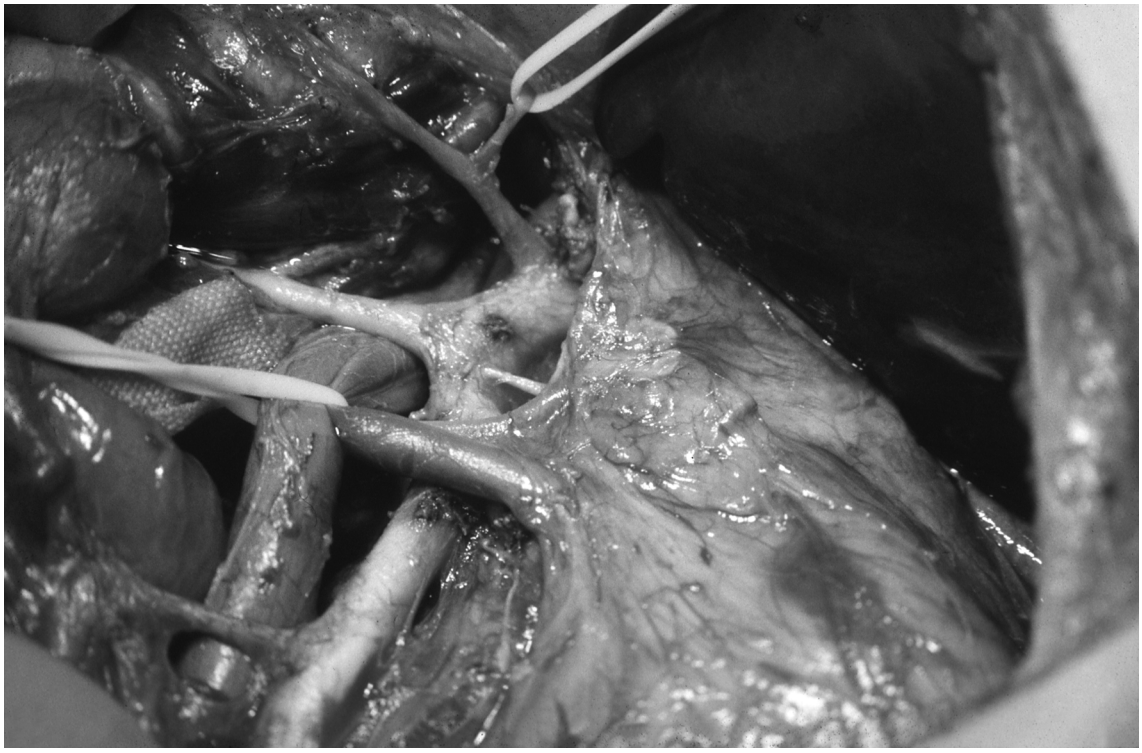

Figure 3 Completed surgical excision.

plane. This establishes the plane of dissection for the remainder of the procedure.

The dissection advances proximally, dividing tumour and adventitia down to the media in 1–2-cm steps. Upward and lateral traction on the tumour assists in displaying the correct plane. Bipolar diathermy is used for haemostasis.

In this manner, the dissection advances to the common iliac artery, then along the distal aorta, always incising along the middle of the artery in the 12 o'clock position.

The first of the major visceral arteries encountered is the inferior mesenteric artery which is characterised by its surrounding leash of small vessels. The dissection skirts the origin of this vessel and proceeds proximally. At the level of the gonadal arteries difficulty may be encountered as these tumours are frequently very adherent in this area.

Proximal to the gonadal vessels, the bluish tinge of the left renal vein is seen as the tumour is divided over it. This vein is usually evident before it is in danger. A segment of vein must be cleared of tumour in order to continue the aortic dissection. This is done in exactly the same manner – longitudinal incision of tumour and adventitia along the middle of the vessel, subsequently clearing the vessel circumference over a 5-cm length.

Once the vein has been mobilised, it may be retracted to continue display of the aorta. The origin of the left renal artery is then sought as this is a guide to the position of the superior mesenteric artery. Once the origin of the left renal artery has been identified, the plane of the dissection is changed from the 12 o'clock to the 2 o'clock position. The blade still comes down on the aortic wall in perpendicular fashion but well lateral to the origin of the superior mesenteric and coeliac arteries.

As the surgeon advances proximally, the median arcuate ligament is encountered and divided. The dissection continues until the superior limit of the tumour is reached.

If the surgeon has reached this stage of the operation whereby part of the aortic wall is visible in continuity from proximal to distal limits of tumour, then the likelihood is that the tumour can be excised.

Placing a sling around the thoracic aorta provides reassurance for the remainder of the operation.

Each of the involved branches of the aorta is dissected in similar fashion. Clearance of the anterior wall of the distal thoracic and upper abdominal aorta will bring the origins of coeliac and superior mesenteric arteries into view. Each of these is then exposed, in turn, from proximal to distal. The coeliac trunk is longer than anticipated, frequently more than 3 cm in length. The tumour and adventitia are incised along the middle of this vessel and then along each of its branches as far as necessary.

Subsequently, the superior mesenteric artery is displayed, although dissection of its branches is rarely necessary as the tumour does not usually extend very far distally.

Table 3 5-year survival by stage

Stage	*n*	(%)
Stage 1	6 of 6	(100)
Stage 2	28 of 29	(97)
Stage 3	24 of 32	(75)
Stage 4	38 of 126	(30)

Table 4 5-year survival related to resection

Stage	Resection	*n*	(%)
Stage 3 disease			
	Complete resection	26 of 29	(86)
	Incomplete resection	2 of 5	(40)
Stage 4 disease			
	Complete resection	30 of 100	(30)
	Incomplete resection	8 of 26	(30.6)

Deep to the artery is the accompanying superior mesenteric vein which is infrequently involved by left-sided tumour.

Clearance of the left renal artery is usually straightforward but if, for some reason, this is not possible, then the right renal artery should be displayed before the decision to perform a left nephrectomy.

The order in which vessels are cleared depends on tumour site and size.

In general, clearance of the aorta follows clearance of the visceral arteries as detailed above. It is not unusual to divide a number of lumbar arteries. It is not clear how many may be divided safely without compromise to the blood supply of the spinal cord. As many as five have been divided with no ill effects but the aim is to preserve as many as possible. The typical appearance following tumour clearance is shown in Figure 3. The coeliac, its branches, superior and inferior mesenteric arteries as well as the inferior vena cava are clearly seen. No remaining tumour is present.

For right-sided tumours, the same principles apply in dissecting the inferior vena cava.

The management of pelvic tumours is similar in regard to blood vessel dissection. The incision used is a modified Pfannensteil incision reaching almost to the level of the anterior superior iliac spine on either side. The tendon of each rectus muscle is divided to detach the muscles from the bone. The muscle layers laterally are divided. On occasion, tumour fills the pelvis and access to the internal iliac vessels is impossible. Under these circumstances, division of the symphysis pubis allows sufficient space to dissect each internal iliac artery in turn.

One or both internal iliac arteries are displayed. The corresponding veins lie more laterally and are generally less troublesome than the arteries.

It is advisable for the surgeon to revise the anatomy of posterior and anterior divisions of the internal iliac vessels. The branches of the posterior division seem constant but the branches of the anterior division are quite variable.

Two nerves may also be encountered. The lumbo-sacral trunk is sought medial to the psoas muscle. It lies lateral to the ascending lumbar artery. The obturator nerve is found quite deep in the pelvis medial to the vessels. These nerves are readily separated from tumour when necessary.

The mode of vascular dissection is the same as described above.

In all patients, we attempt to preserve at least one hypogastric nerve in order to preserve ejaculation. This is not always possible, especially with pelvic tumours.

Results

Macroscopic complete or near complete (greater than 95%) excision was achieved in 89% of those with abdominal disease. Sixteen of 17 (94%) of those with pelvic tumours underwent complete excision.

Five-year survival by stage is shown in Table 3. Five-year survival figures for those with stages 3 and 4 disease are shown in Table 4.

Two children died after operation. The first of these, a 4-year-old boy, had complete excision of a large stage 4 tumour and received a 3-l transfusion during the operation. When sudden deterioration occurred 24 h later, his blood sugar was 0 mmol/l. He died soon afterwards with severe brain damage. Our understanding is that the glucose load associated with the large transfusion was followed by rebound hypoglycaemia.

The second death was in a 3-year-old boy with stage 4 disease who collapsed on the eighth postoperative day with rupture of his aorta and splenic artery. Although control of the bleeding was achieved, he died a few days later. His aorta had ruptured just above the level of the gonadal arteries. It seems likely that the wall of aorta had been excessively thinned by the excision. The cause of the splenic artery rupture was unclear.

Postoperative diarrhoea was a problem in about 30% of those who had undergone clearance of coeliac and superior mesenteric arteries. In survivors, the diarrhoea has persisted in the majority.

It is common to see substantial lymphatic leakage during the course of the operation. Pronounced ascites in the immediate postoperative period is common but almost always resolves within 7 days. Three children required insertion of a peritoneo-venous shunt because of persisting severe distension. These shunts proved highly effective and all were removed uneventfully and without recurrence of ascites more than 1 year from the time of insertion.

Adhesion obstruction has been less common than might have been anticipated. Five children required operative division of adhesions.

In 11% of the total, tumour could not be removed. Factors associated with failure included invasion of tunica media, gross involvement of the portal triad, fresh tumour growth at the time of operation and dense calcification precluding incision of the tumour.

Three aortic injuries occurred which required formal patch repair. In one, the operation was abandoned at that time and completed at a second sitting some months later. Thus far, no injuries have occurred to coeliac or superior mesenteric arteries.

Troublesome caval injury was not encountered. On occasion, the left renal vein was sacrificed without any effect on renal function, as long as the kidney was left undisturbed and the hilum was not dissected.

Late loss of a kidney due to apparent renal vein thrombosis occurred in one child. No other kidneys are known to have been lost to arterial or venous thrombosis.

The effects of the operation on potency and ejaculation are unclear. To date, in the long-term follow-up clinic, no boys have admitted to any problems in this regard.

As details of biological markers have only recently become available, the effect of these factors on resectability and outcome have not been evaluated.

Discussion

The advent of more effective chemotherapy presents paediatric surgeons with a new problem, potentially requiring a new solution. Standard methods of dissection using forceps or scissors to separate tissue prior to division appeared unduly hazardous as the required plane of dissection is potential rather than real. As the tips of the instrument are out of sight when using this form of dissection, this method has little appeal. With sharp dissection, the scalpel blade is always in view and the plane is dissected in continuity. The technique described here allows tumour excision in the majority but fails in a number.

The use of the ultrasound dissector has been advocated but the author has found it unhelpful in practice, as the plane chosen by the dissector is slightly remote from the vessel wall.

A failure rate of 11% is substantial. This failure rate has remained fairly constant over the period of this review. As the main reason for failure has been invasion of the tunica media of the aorta, it is not clear that a different technique will achieve a better result.

A small number of older children (over 10 years of age) with neuroblastoma have also been encountered. In those children who have encasement of major vessels, the surgery has been unusually difficult as the tumours have been extremely hard in consistency and difficult to dissect from the vessels.

Wound problems have been infrequent. As most wound infections present after discharge, there are no data on this particular complication.

In the first few years of the development of this technique, it was not our practice to monitor blood sugar routinely in children over the age of 12 months. Since the death related to hypoglycaemia, we have routinely monitored blood sugar on a 4–6 hourly basis. We have encountered two further children who developed hypoglycaemia, one on a temporary basis and the other on a permanent basis. This latter child was found to have absence of adrenal function on subsequent evaluation, although one adrenal was still *in situ* and apparently healthy.

Postoperative diarrhoea is common in those who have undergone dissection of coeliac and superior mesenteric arteries. We attribute this to removal of the inhibitory sympathetic nerve supply to the gut.[15] The diarrhoea may be quite troublesome but does not affect growth adversely. Loperamide is at least partially effective in the majority. The problem has persisted in long-term survivors.

We attribute the relative infrequency of adhesion obstruction to the use of an intestinal bag and to the exaggerated peristalsis which follows clearance of the sympathetic nerve supply to the gut. There is, of course, an additional risk associated with denervation of the intestine. Intestinal colic will not be felt by these children and there is a risk that adhesion obstruction will not be recognised at an early stage.

At least one of the hypogastric nerves is divided in the majority of children undergoing this operation. We have sought evidence of impotence or problems with ejaculation in the long-term follow-up clinic. Although no formal assessment has been carried out, all the boys who have been questioned deny having such problems. It is inconceivable that all will be trouble-free but the scale of the problem remains to be defined.

The removal of the sympathetic fibres from the vessels on one side usually results in a difference in temperature of the lower limbs and feet. The affected side is generally warmer and pinker in colour. On occasion, there has been concern that the other limb is ischaemic.

Only a handful of children have undergone pelvic symphysiotomy. We have been unable to detect any untoward consequences. The access provided by this manoeuvre has

been vital and has enabled tumour clearance which would otherwise have been impossible.

From these and other results, complete excision of stage 1–3 disease conferred a survival advantage.[5,14] The same cannot be said with any confidence for those with stage 4 disease. At the present time, no prospective randomised trial has evaluated the role of surgery in these children. The figures reported here do not suggest that complete excision confers a survival advantage but the tumours which were removed cannot necessarily be compared with those which were not. This is an on-going debate in paediatric surgery and recent figures suggest that complete excision in these children, may confer a survival advantage.[9,10] At the present time, all the major paediatric oncology groups include an attempt at complete excision in their treatment protocols.

Conclusions

The technique reported here allows a planned, systematic and consistent approach to resection, regardless of the position of the tumour. It is easily taught and learned and has enabled excision of the majority of tumours.

Acknowledgement

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References

1. Stiller CA, Parkin DM. International variations in the incidence of neural crest tumours. *Int J Cancer* 1992; **52**: 538–43.
2. Gross RE, Farber S, Martin LW. Neuroblastoma sympatheticum: a study and report of 217 cases. *Pediatrics* 1959; **23**: 1179–91.
3. Brodeur GM, Pritchard J, Berthold F, Carlsen NL, Castel V, Castelberry RP *et al*. Revisions of the international criteria for neuroblastoma diagnosis, staging and response to treatment. *J Clin Oncol* 1993; **11**: 1466–77.
4. Brodeur GM, Castleberry RP. Neuroblastoma. In: Pizzo PA, Poplack DG. (eds) *Principles and Practice of Pediatric Oncology*, 4th edn. Philadelphia, PA: Lippincott, Williams and Wilkins, 2001.
5. Ikeda H, Iehara T, Tsuchida Y, Kaneko M, Hata J, Naito H *et al*. Experience with International Neuroblastoma Staging System and Pathology Classification. *Br J Cancer* 2002; **86**: 1110–6.
6. Grosfeld JL, Baehner RL. Neuroblastoma: an analysis of 160 cases. *World J Surg* 1980; **4**: 29–38.
7. Stiller CA. Trends in neuroblastoma in Great Britain: incidence and mortality, 1971–1990. *Eur J Cancer* 1993; **29A**: 1008–12.
8. Powis M, Ineson JD, Holmes SJ. The effect of complete excision on stage III neuroblastoma: a report of the European Neuroblastoma Study Group. *J Pediatr Surg* 1996; **31**: 516–9.
9. Adkins ES, Sawin R, Gerbing RB, London WB, Matthay KK, Haase GM. Efficacy of complete resection for high-risk neuroblastoma: a Children's Cancer Group study. *J Pediatr Surg* 2004; **39**: 931–6.
10. La Quaglia MP, Kushner BH, Su W, Heller G, Kramer K, Abramson S *et al*. The impact of gross total resection on local control and survival in high-risk neuroblastoma. *J Pediatr Surg* 2004; **39**: 412–7.
11. Azizkhan RG, Shaw A, Chandler JG. Surgical complications of neuroblastoma resection. *Surgery* 1985; **97**: 514–7.
12. Kiely EM. The surgical challenge of neuroblastoma. *J Pediatr Surg* 1994; **39**: 128–33.
13. Rees H, Markley MA, Kiely EM, Pierro A, Pritchard J. Diarrhoea after resection of advanced abdominal neuroblastoma: a common management problem. *Surgery* 1998; **3**: 568–72.
14. Evans AE, Silber JH, Shpilsky A, D'Angio GJ. Successful management of low-stage neuroblastoma without adjuvant therapies: A comparison of two decades, 1972 through 1981 and 1982 through 1992, in a single institution. *J Clin Oncol* 1996; **14**: 2504–10.